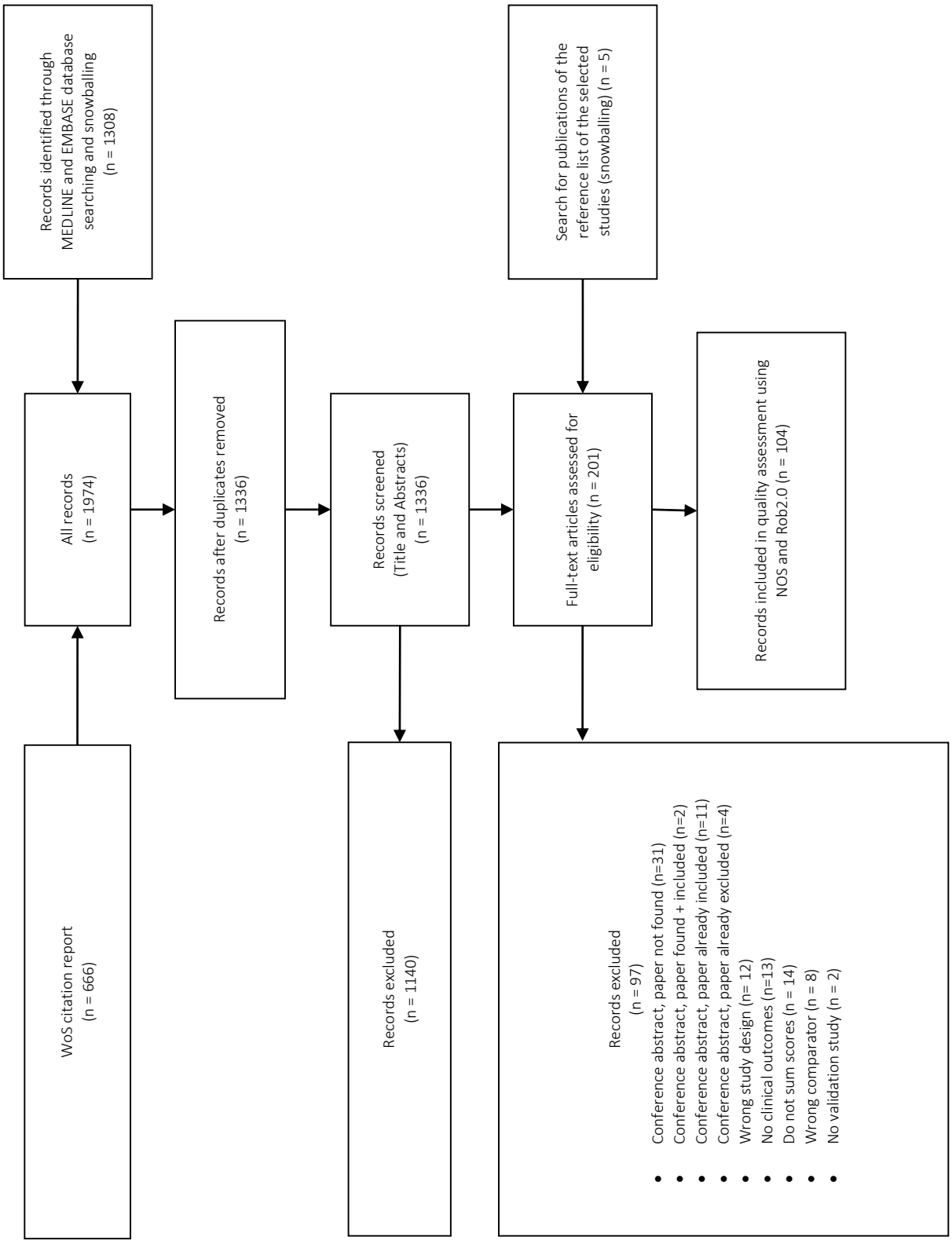
Quality of anticholinergic burden scales and their impact on clinical outcomes - a systematic review, EJCP, Lisibach A et al, Corresponding author: Pr Chantal Csajka, Center for Research and Innovation in Clinical Pharmaceutical Sciences, Rue du Bugnon 17, 1005 Lausanne

Appendix 1: Search queries used in MEDLINE and EMBASE for the identification of all published ABS.

MEDLINE search query: ("anticholinergic"[Title] OR "anticholinergics"[Title]) AND ("scale"[Title] OR "risk scale"[Title] OR "scales"[Title] OR "properties"[Title] OR "score"[Title] OR "scores"[Title] OR "risk scales"[Title] OR "activities"[Title] OR "activity"[Title] OR "burden scale"[Title] OR "burden scales"[Title] OR "load"[Title] OR "burden"[Title] OR "effect"[Title] OR "effects"[Title]) AND "humans"[MeSH Terms] AND (French [lang] OR German[lang] OR English[lang])

EMBASE search query: (anticholinergic:ti OR anticholinergics:ti) AND (scale:ti OR 'risk scale':ti OR scales:ti OR properties:ti OR score:ti OR scores:ti OR 'risk scales':ti OR activities:ti OR activity:ti OR 'burden scale':ti OR 'burden scales':ti OR load:ti OR burden:ti OR effect:ti OR effects:ti) AND ([english]/lim OR [french]/lim OR [german]/lim) AND [humans]/lim

Appendix 2: Detailed PRISMA flowchart for the identification of all validation studies for the identified ABS.



Appendix 3: The adapted AGREE II tool to assess the quality of the identified ABS.

There are 6 domains, every single item (numbered) below is graded from 1 to 7 by each researcher.

score 1 = strongly disagree (no information relevant on the respective item/ if it's reported very poorly)

score 2 - 6 = reporting doesn't meet the full criteria (score increases as more considerations are addressed

score 7 = strongly agree (in case reporting quality is exceptional, all criteria & considerations are met)

For the scoring, the numbered items in the LEFT column are the topics to be rated with signaling *questions* below.

The points with boxes in the column in the RIGHT column assist the scoring and could be identified.

CHECKLIST ITEM AND DESCRIPTION	**REPORTING CRITERIA**	**Grade**
BASIC INFORMATION OF THE SCALE		
TITLE OF THE PUBLICATION		
YEAR OF PUBLICATION		
COUNTRY OF DEVELOPED SCALE		
ABBREVIATION OF SCALE		
DOMAIN 1: SCOPE AND PURPOSE (Total: max. 21 P)		
1. OBJECTIVES *Report the overall objective(s) of the paper. The expected health benefits from the developed scale are to be specific to the clinical problem/ health topic. Additionally: is it well written, clear and concise.*	☐ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☐ Expected benefit(s) or outcome(s) ☐ Target(s) (e.g., patient population, society)	
2. QUESTIONS *Report the health question(s) covered by the work, particularly for the key recommendations. Additionally: is it well written, clear and concise?*	☐ Target population ☐ Intervention(s) or exposure(s) ☐ Comparisons (if appropriate) ☐ Outcome(s) ☐ Health care setting or context	
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the scale is meant to apply. Additionally: is it well written, clear and concise.*	☐ Target population, sex and age ☐ Clinical condition (if relevant) ☐ Severity/stage of disease (if relevant) ☐ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	

DOMAIN 2: STAKEHOLDER INVOLVEMENT (Total: max. 14 P)		
4. GROUP MEMBERSHIP *(This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.)* *Do they report all individuals who were involved in the development process (expert panel)?* *Do they mention them by:* *Is there a minimum of 2 different researchers with two different backgrounds (e.g physician and clinical pharmacists)?*	☐ Yes ☐ No ☐ Not mentioned Name, by disciple /content expertise, institution, geographical location, role in the scale development group ☐ Yes ☐ No Expert panel number: _____ *Expert panel:* ☐ General physician ☐ Geriatric physician ☐ Clinical pharmacist ☐ Nurse ☐ Researcher ☐ Biologist ☐ Other * * Other:_____	
5. TARGET USERS *Report the target (or intended) users of the scale. Additionally: is it well written, clear and concise.* *Is it well stated who is intended to use the scale? (specify, e.g. clinical pharmacists, physicians, nurses, patients)* *Does it also mention how to be used by the target audience?*	☐ Yes ☐ No ☐ Yes ☐ No	
DOMAIN 3: RIGOUR OF DEVELOPMENT (Total: max. 63 P, Item 7 + 11 count double)		
6. SEARCH METHODS *Do they report details of the strategy used to search for evidence for anticholinergic activity of a certain substance?* *If yes, what is reported?* *Additionally: Is the search relevant and appropriate to answer the health question.*	☐ Yes ☐ No ☐ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☐ Time periods searched (e.g., January 1, 2004 to March 31, 2008)	

Is there enough information provided for anyone to replicate the search?	☐ Search terms used (e.g., text words, indexing terms, subheadings) ☐ Full search strategy included (e.g., possibly located in appendix) ☐ Other literature* e.g. Martindale, Compendium Specify other Literature*:_____	
7. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.* *(Each criterion included goes one point up the scale from 1 to 7)*	☐ Serum anticholinergic activity ☐ Pharmacokinetic / substance properties ☐ Anticholinergic side effects ☐ Blood-brain-barrier permeability of substance ☐ Taking dosage into account ☐ Route of administration was considered ☐ Clinical expert opinions ☐ Scale is based on previous published scale (includes reviews as well, e.g. Durán)	
8. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths/limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Statements highlighting the strengths/limitations of the evidence should be provided. This ought to include explicit descriptions - using informal or formal tools/methods - to assess and describe the risk of bias for individual studies and/or for specific outcomes and/or explicit commentary of the body of evidence aggregated across all studies. This may be presented in different ways, e.g: tables commenting on different quality domains; the application of a formal instrument or strategy; or descriptions in the text.*	☐ Several sources (e.g. in vitro and in vivo) ☐ Also clinical data (ADR) ☐ Quality assessment of the studies/data ☐ Consistency of results across studies/data ☐ Study design included in body of evidence ☐ Number of drugs that were evaluated ☐ Are all relevant drug classes included? ☐ Language: was the evidence not limited by the language?	
9. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.* *Was a clear scoring rule developed?*	☐ Yes ☐ No	

Do they reason their scoring?	☐ Yes ☐ No	
Scoring was performed by 2 or more independent researchers?	☐ Yes ☐ No	
Were there no discrepancies?	☐ Yes ☐ No	
If yes, do they mention how they resolved them?	☐ Yes ☐ No	
10. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☐ Is there a clear link between the recommendation (e.g. classification) of a drug and the evidence? Is the classification reproducible?	
11. VALIDATION OF SCALE *Has the scale been validated?*	☐ Yes ☐ No	
Were the studied primary and secondary outcomes appropriate?	☐ Yes ☐ No	
What was the studied outcome of the external review? Was it clinical?	_____	
12. UPDATING PROCEDURE *Describe the procedure for updating the work.* *Has there been an update since the development of the scale?* *If yes, when? (Was it provided by the authors?)*	☐ Yes * ☐ No * Update: _____	

DOMAIN 4: CLARITY OF PRESENTATION (Total: max. 14 P)		
13. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☐ A statement of the recommended action ☐ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☐ Relevant population (e.g., patients, public) ☐ Caveats or qualifying statements, if relevant (e.g., patients or conditions to whom the recommendations would not apply) ☐ If there is uncertainty about the best care option(s), the uncertainty should be stated.	
14. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.* *Is a full list of scored drugs available?* *It is clearly described, how to use the scale? (clinical or research practice)*	☐ Yes ☐ No ☐ Yes ☐ No	
DOMAIN 5: APPLICABILITY (Total: max. 7 P)		
15. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☐ Additional materials to support the implementation of the scale in practice. o Web calculator of score o List with anticholinergic drugs provided o Links to how-to manuals o Solutions linked to barrier analysis (Item 18) o Tools to capitalize on facilitators (Item 18)	
DOMAIN 6: EDITORIAL INDEPENDENCE (Total: max. 21 P)		
16. FUNDING BODY *Report the funding body's influence on the content of the scale.*	☐ The name of the funding body or source of funding (or explicit statement of no funding) ☐ A statement that the funding body did not influence the content of the scale	
17. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests. Have there been any competing interests?*	☐ Yes ☐ No	

18. SUGGESTIONS FOR FURTHER RESEARCH *Do they suggest further research?* *Or is there profound explanation why such research isn't required currently?*	☐ Yes ☐ No * * Explanation:_____ _____	
DOMAIN 7: OVERALL SCALE ASSESSMENT (Total: max. 14 P)		
19. RATING OF THE OVERALL QUALITY OF THE SCALE *Rate the scale in a total overview from 1 (lowest possible quality) to 7 (highest possible quality).*	☐ It is of poorest quality (1) ☐ The quality should be improved in certain aspects (2-6) ☐ Quality is exceptional (7)	
20. RECOMMENDATION FOR USE *Decide whether the scale could be recommended for good results, or not.*	☐ Yes ☐ Yes, with modifications ☐ No	
Comments:		

From: Brouwers MC, Kerkvliet K, Spithoff K, on behalf of the AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016;352:i1152. doi: 10.1136/bmj.i1152.

For more information about the AGREE Reporting Checklist, please visit the AGREE Enterprise website at http://www.agreetrust.org.

Appendix 4: The slightly adapted NOS tools for case-control, cohort studies and cross-sectional studies used for the quality assessment of each validation studies. The dot indicates a star.

Case-control studies	**Cohort / Cross-sectional studies**
Selection	**Selection**
1) Is the case definition adequate?	***1) Representativeness of the exposed cohort***
a) yes, with independent variables ●	a) truly representative of the average … (describe) in the community ●
b) yes, e.g. record linkage or based on self-reports	b) somewhat representative of the average … (describe) in the community ●
c) no description	c) selected group of users eg nurses, volunteers
	d) no description of the derivation of the cohort
2) Representativeness of the cases	***2) Selection of the non-exposed cohort***
a) consecutive or obviously representative series of cases ●	a) drawn from the same community as the exposed cohort ●
b) potential for selection bias or not stated	b) drawn from a different source
	c) no description of the derivation of the non-exposed cohort
3) Selection of controls	***3) Ascertainment of exposure / Measurement method of exposure***
a) community controls ● (same population)	a) secure record (eg surgical records) ● / validated measurement tool ●
b) hospital controls	b) structured interview ● / some measurement tool ●
c) no description	c) written self-report
	d) no description
4) Definition of controls	***4) Demonstration that outcome of interest was not present at start of study or baseline measurement / Always "no" in cross-setional***
a) no history of disease (endpoint) ●	a) yes ●
b) no description of source	b) no
Comparability	**Comparability**
1) Comparability of cases and controls on the basis of design or analysis	***1) Comparability of cohorts on the basis of the design or analysis***
a) study controls for… (select the most important factor) ● Identified most important factor: (write down for each study)	a) study controls for… (select the most important factor) ● Identified most important factor: (write down for each study)
b) study controls for any additional factor (could be a second most important factor) ● Identified factor: (write down for each study)	b) study controls for any additional factor (could be a second most important factor) ● Identified factor: (write down for each study)

Exposure	**Outcome**
1) Ascertainment of exposure	***1) Ascertainment of outcome***
a) secure records (e.g surgical records) ●	a) independent blind assessment ●
b) structured interview where blind to case/ control status ●	b) record linkage ●
c) interview not blinded to case / control status	c) self-report
d) written self-report or medical record only	d) no description
e) no description	
2) Same method of ascertainment for cases and controls	***2) Was follow-up long enough for outcomes to occur / Always "no" in cross-setional***
a) yes ●	a) yes ●
b) no	Selected adequate time of follow-up
3) Missing data	***3) Adequacy of follow up of cohorts / Missing data for cross-sectional***
a) described how much missing data and how they handled it ●	a) complete follow up - all subjects accounted for ● / no missing data ●
b) mention missing data but no further explanation	b) subjects lost to follow up unlikely to introduce bias: < 10 (20%)% (Oxford Center of EBM) ● / described how much missing data and how they handled it ●
	Adequate number: *If <20% of subjects were lost to follow-up but the difference between the groups is large consider downgrading to c, especially if no reason is given*
c) no description	c) follow-up rate < 80 % and not description of those lost / mention missing data but no further explanation
	d) no statement / no description

Appendix 5: AHRQ standards conversion rules for the quality assessed by the NOS and Rob2.0.

Quality assessed by the NOS for cohort, case control and cross-sectional studies:
Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Quality assessed by the Rob2.0 for RCT studies:
Good quality: low risk of bias for each domain and all criteria met
Fair quality: high risk of bias for one domain or two criteria unclear risk of bias
Poor quality: two or more criteria listed as high or unclear risk of bias